RNA Polymerase II: Reading in Loops to get Different Tails

Abstract
The DNA-loops are necessary to recycle the RNA polymerase for the multiple transcription rounds of a gene. The nascent transcript needs to be 3’-end processed: cleaved in a specific position and added a 3’-end poly-(A)-tail to become an mRNA. Under regulated conditions, genes undergo 3’-end RNA processing at different positions. This is called alternative polyadenylation (APA) and, as a consequence, mRNA molecules could have different stabilities and regulated fates. The formation of alternative DNA loops is a key factor in order to get the APA.

Keywords: RNA Polymerase; Transcription; Alternative polyadenylation; DNA loops

Comment
The RNA polymerase II is the multi-subunit enzyme able to transcribe the protein-encoding genes in eukaryotic cells producing the messenger RNA (mRNA). Two critical steps in eukaryotic mRNA biogenesis, for its correct 3’-end processing are: cleavage and polyadenylation. This is necessary to achieve a message that can be recognized by the proteins that properly export it to the cytosol and so that it can be efficiently translated by the ribosomes or mediate its turnover [1,2].

But what happens with the RNA polymerase after a first round of transcription? It is necessary to recycle the RNA polymerase back to the promoter for a new round of transcription. For this last purpose, the formation of DNA-loops, establishing physical interactions between the promoter and the sequences downstream from the coding region, are necessary [3-6]. The current view is that these loops are transcriptional memories for the cells.

However, it is not that simple, the major subunit of the RNA polymerase II has a Carboxy-Terminal Domain (CTD) with multiple repeats of a seven amino-acid sequence (YSTPSPS), each position can be covalently modified and there are multiple combinations possible. This was named as the CTD Code by Buratowski, a term currently in use [7-10]. CTD is considered as a recruitment platform for the different factors that are associated to the enzyme during initiation, elongation or the steps related to splicing, transcriptional termination and RNA processing. While riding the loop the polymerase will undergo multiple changes in the CTD Code and, to finally be recycled back to the promoter, its CTD must be hypo-phosphorylated.

Things become more complicated by the fact that many genes are under alternative 3’-end processing (alternative polyadenylation, APA) [11-13]. One of these genes is the yeast KICYCL gene [14,15]. The regulated APA for this gene causes two transcripts with different 3’-UTR lengths. We have recently shown in the related article of this comment that for genes with regulated APA there is alternative DNA-loops formation also. Moreover, the predominant processing region is included in the predominant loop. Changes in RNA polymerase II positioning or the CTD phosphatase Ssu72 also correlate with both, the loop and APA predominance [16]. From the data attained for a gene with APA, it is clear the dependence of RNA processing in DNA-loop formation and, as indicated in the title, the RNA polymerase has to read the different loops in order to get messages with different tails which will depend on the cellular requirements.
References